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14. ABSTRACT

Purpose: To examine neuropsychological outcomes associated with OIF deployment among regular Active Duty and activated National Guard Army Soldiers. Secondary objectives include identification of both deployment-related and non-deployment-related risk and resiliency factors for adverse neuropsychological outcomes. Scope: Prospective cohort design in which deploying Soldiers are assessed once prior to deployment and twice after redeployment. A comparison group of Soldiers is assessed before and after a period of garrison duty. Methods include administration of performance-based neuropsychological measures and self-report surveys. Progress: Data will be linked to environmental monitoring data. Time 1 and Time 2data were collected on all but one small non-deployed unit. Time 3 data have been collected on 2 brigade-level active duty units. Major findings: Preliminary analyses indicate that OIF deployment is associated with declines in memory and attentional performance and increased emotional distress but with improvement in simple reaction time.

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deployment health, neuropsychology, cognitive functioning, stress, environmental hazards, Iraq

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INTRODUCTION

Unexplained health symptoms appear to be ubiquitous to modern war.[1] However, questions remain regarding linkages between military operational deployment and the development of physical or mental health symptoms. An area of particular vulnerability may be neuropsychological functioning. For example, following the 1991 Gulf War (GW), significant subsets of military personnel and veterans reported non-specific health (e.g., headache, fatigue) and cognitive (e.g., memory impairment) symptoms suggestive of possible neural dysfunction.[3-7] Neuropsychological functioning encompasses cognitive (e.g., memory, attentional, reasoning), perceptual-sensory-motor (e.g., motor speed), and emotional (e.g., mood) behaviors thought to reflect neural integrity. Unresolved issues include whether subjective neuropsychological complaints correspond to objectively measured indices; whether neuropsychological problems can be linked to specific environmental exposures, stress exposures, or other deployment-related experiences; and the interaction of deployment with potential risk and resilience factors on neuropsychological functioning.

The work encompassed in this report is now referred to as the Neurocognition Deployment Health Study (NDHS). To help address the gaps in knowledge described above, the NDHS incorporates prospective administration of performance-based measures of neuropsychological functioning in cohorts of Army Soldiers deploying in support of Operation Iraqi Freedom (OIF) and in a similar group of Soldiers before and after an interval of non-deployment. The objectives of this ongoing study are to (a) examine the impact of combat-zone deployment on neuropsychological outcomes, including neurobehavioral and emotional functioning, (b) examine the impact of deployment-related stress and environmental exposures on neuropsychological outcomes, and (c) identify potential health risk and protective factors relevant to neuropsychological outcomes. A secondary objective of the study is to describe select psychiatric outcomes, the importance of which is suggested by high rates of PTSD and other psychiatric disorders following Iraq deployment.[2]

BODY

Project History

The original SOW described the following elements within a 24-month timeframe:

YEAR 1	Phase I	
Task 1	Proposal phase and Week 1	Orient project staff to project tasks, training, set-up
Task 2	Months 1-4	Phase I pre-deployment, baseline assessment & data collection, creation of database
Task 3	Months 5-8	Collection of electronic medical/health care record system databases through data requests, transfer of test data to formats readable by statistical software; data entry
Task 4	Months 9-12	Preliminary analyses of Phase I data collection.
YEAR 2	Phase II	
Task 1	Months 1-4	Post-deployment assessment & data collection; collection of electronic deployment-related service information through data requests; data transfer; data entry
Task 2	Months 5-7	Complete collection of electronic deployment-related service information, data transfer, and data file linking of pre- and post- databases.
Task 3	Months 8 – 12	Final data analysis; preparation of reports

However, the SOW was later approved to extend to a 48-month time frame. The 48-month time frame reflects in part modifications to the data collection schedule associated with the deployment rotations of the military units included in the study and initial delays in the study associated with administrative approvals and identification of appropriate military units. In addition, it reflects the addition of a third data collection point for each unit so that longitudinal stability may be assessed and outcomes expanded to include health behaviors and occupational functioning.

The history of the project is as follows:

Nov 02:	Proposal submitted
Dec 02:	Made contact with US Army Forces Command (FORSCOM) Surgeon's Office
Jan 03:	FORSCOM requests Department of Army letter of support
28 Jan 03:	Final HSRRB approval
31 Jan 03:	MRMC Commander provides DA letter of support
28 Feb 03:	FORSCOM identifies initial units (primarily regular Active Duty, Fort Hood); III Corps requests FORSCOM tasking order
Mar 03:	Start-up funds received
Mar 03:	Assistant Secretary of Defense provides letter of support FORSCOM tasks III Corps Scheduled by III Corps to begin data collection 27 Mar
22 Mar 03:	4th Infantry Division receives flight orders/opts out of study
3–9 Apr 03:	301 "deploying" Soldiers (1st Cavalry Division) assessed (Time 1)
14–18 Apr 03:	149 "non-deploying" Soldiers assessed
14 Apr 03:	Deployment orders of 1CD called into question (eventually cancelled)
Aug 03:	FORSCOM identifies two Active Duty Stryker brigades appropriate to study 3/2 SBCT to serve as deploying group; 1/25 SBCT to serve as non-deploying group Intent to deploy 1st Cavalry Division announced
Nov 04:	3/2 SBCT deploys
22 Sep- 9Oct03:	450 3/2 SBCT and 387 1/25 SBCT Soldiers assessed (Time 1)
Dec 04:	2nd baseline (Time 1.5) conducted on 1st Cavalry Soldiers to provide assessment more proximal to actual deployment
Feb 04:	1st Cavalry deploys
May 04:	Intent to deploy 1/25 SBCT announced; Time 2 assessment (post-garrison duty) conducted FORSCOM identifies 278th ARNG unit as appropriate National Guard study component
July 04:	Soldiers from 1/25 SBCT not available in May 04 assessed 278th ARNG assessed (Time 1)
Sep 05:	1/25 SBCT deploys
Nov 05:	3/2 SBCT returns
Dec 05:	278th ARNG deploys (1 month earlier than originally anticipated) To provide an Active Duty comparison that was deployed contemporaneously with ARNG unit, plans are made to assess 1/25 SBCT upon their return.
Jan 05:	Post-deployment assessment conducted on 3/2 SBCT
Mar 05:	1st Cavalry returns
May 05:	Post-deployment assessment conducted on 1st Cavalry and other III Corps units
Aug 05:	Plans made to assess 3/2 SBCT (Time 3) in Sept 05 Katrina displaces New Orleans study team, preventing travel; Sept assessment rescheduled to Dec 05
Oct 05:	Major study equipment retrieved from New Orleans
Dec 05:	Time 3 (follow-up post-deployment assessment conducted on 3/2 SBCT)
Jan 06:	Time 3(initial post-deployment survey) conducted on 1/25 SBCT (unit formerly a non-deployed comparison during the Time 1 to Time 2 interval)
April 06:	Time 2 (post-deployment) assessment of ARNG unit
May 06:	Time 2 (post-deployment) assessment of ARNG unit
Jun 06:	Time 2 (post-deployment assessment of ARNG unit
Jun 06:	1st Cav. tasked by FORSCOM for Aug 06 Time 3 (follow-up) assessment

The current timeline now includes Time 2 primary data collection through April 2006, Time 3 primary data collection through October 2006, and Time 3 administrative data collection, data analysis and preparation of final reports extending through January 2007. Therefore the final, approved SOW is as follows:

STUDY TIMETABLE –MODIFIED STATEMENT OF WORK

YEAR 1		
Task 1	Proposal phase and Week 1	Orient project staff to project tasks, training)
Task 2	Months 1-3	Set-up and baseline (Time 1) assessment of Ft. Hood participants
Task 3	Months 4-10	Establish data base; as relevant to Task 2 participants, collection of electronic medical/health care record system databases through data requests, transfer of test data to format readable by statistical software; data entry of data generated by Task 2
Task 4	Months 6-12	Re-assessment of Ft. Hood participants to correspond more closely to their rescheduled deployment date; baseline (Time 1) assessment of Ft. Lewis participants (3/2 Stryker Brigade Combat Team (SBCT); 1/25 Stryker Brigade Combat Team (SBCT);
YEAR 2		
Task 1	Months 13-18	As relevant to Task 4 participants, collection of electronic medical/health care record system databases through data requests, transfer of test data to format readable by statistical software; data entry of data generated by Task 4
Task 2	Months 13-24	Collection of Time 2 data relevant to Ft. Lewis participants
Task 3	Months 13-24	Collection of Time 1 data; deploying National Guard cohort
YEAR 3		
Task 1	Months 25-26	Collection of postdeployment data; Fort Hood participants
Task 2	Months 27-36	Collection of electronic medical/health care record system databases through data requests, transfer of test data to format readable by statistical software; data entry of data generated; data analysis and preparation of reports on all participants included in protocol to date.
Task 3	Months 34-36	Collection of Time 3 data on Fort Lewis participants
Year 4		
Task 1	Months 37-39	Collection of Time 3 (2^{nd} post-deployment) data on Fort Hood participants
Task 2	Months 37-39	Collection of post-deployment data on National Guard participants
Task 3	Months 40-44	Collection of electronic medical/health care record system databases through data requests, transfer of test data to format readable by statistical software; data entry of data generated relevant to Year 3, Task 3 and Year 4, Task 1 participants.
Task 4	Months 44-45	Collection of Time 3 data on National Guard participants
Task 5	Months 46-48	Collection of electronic medical/health care record system databases through data requests, transfer of test data to format readable by statistical software; data entry of data generated relevant to Year 4, Task 3 participants. Data analysis and preparation of final reports.

Progress to date

Progress to date includes accomplishment of all tasks through Year 3, as well as Year 4, Task 2. Year 4, Task 1 is tasked to scheduled in August, 2006. Year 4, Task 3 is ongoing. Year 4, Task 4 will likely necessitate a requested SOW modification. Specifically, because of the deployment dates and available week-end drills in which to conduct the Time 2 assessments, Time 2 assessments were completed April – June 06. Thus, it is likely that Time 3 assessments will occur at earliest Dec 06, pushing back Task 5, as well. In addition to the elements explicitly listed within the SOW, we have also established an administrative infrastructure, obtained all necessary administrative approvals, and established a Scientific Advisory Council, which meets annually. A manuscript describing the rationale of the study and the methods was published by *Military Medicine* in 2006 (Vol. 171, 253-260). (Please see Appendix).

All data collected to date have been entered and subjected to intensive data quality checks. Data management has required extensive effort because of the anomalies regarding participant classification as "deployed" or "non-deployed" and the addition of a second baseline for the 1st Cavalry unit. However, a comprehensive and synthesized data base had been established. Primary outcomes for Time 1 to Time 2 have been conducted for the Active Duty component. We are currently in the process of conducting preliminary analyses relevant to secondary objectives (PTSD outcomes) for Time 1 to Time 2 Active Duty comparisons.

Time 1 enrollment totaled 1595 participants. Longitudinal retention for Active Duty Soldiers has been approximately 75.5%. Among those who were not retained for Time 2 assessment, the primary reasons for loss to follow-up have been changes in military unit assignments (14%) and separation from service (46.1%). We are in the process of attempting to contact these participants by phone and mail. Longitudinal retention of National Guard Soldiers has been lower (50-60%) and reflects re-organization within the 278th and, more often, separation from the National Guard. With one state (WI) unit, we arranged a second data collection trip to target Soldiers from a different unit to which some of the participants had been re-assigned. We are attempting to arrange a similar trip with the TN component of the 278th. Like the Active Duty units, we also plan to try to contact individuals by phone and mail.

Unit membership for the original Time 1/Time 2 Active Duty deploying units has been submitted to the US Army Center for Health Promotion and Preventive Medicine to facilitate obtaining appropriate linked environmental data. We are currently summarizing such information to submit for the National Guard units and the active duty unit that deployed between Time 2 and Time 3.

Findings to date

Please see Appendix C for tables summarizing the participant characteristics. In summary, to date we have focused on examination of primary outcomes as a function of deployment. Findings from multi-level analyses that take into account battalion-level unit membership and demographic covariates indicate that deployment was associated with adverse changes to memory functioning (as measured by a non-computerized word list learning task, WMSIII Verbal Paired Associates I sum and a visual reproduction task, WMS Visual Reproductions delay and savings ratio) and attention (as measured by number of non-response errors on a computerized simple continuous performance task, NES3 CPT), but positive improvements in efficiency on a reaction time task (ANAM Simple Reaction Time). All other tasks of cognitive efficiency (ANAM) were unaffected. These findings held even when demographics and estimates of native intellectual potential were taken into account statistically. Additionally, deployment was associated with adverse changes in emotional functioning, including symptoms associated with posttraumatic stress disorder (PTSD) and state affect, including POMS Confusion and Tension scores. In contrast, deployment was not associated with changes in measures of state (POMS) depression, vigor, anger, or fatigue, or measures of functional health (SFv12 and MOS Cognitive) including self-perceptions of cognitive, emotional, and physical functional impact.

These findings have been submitted as a manuscript and slated for publication in the *Journal of the American Medical Association*. We anticipate publication by the end of August 2006.

The next steps in the analyses will be: (1) examination of PTSD as a secondary outcome; (2) examination of factors that predict outcomes within the deployed sample (addressing questions of risk and resiliency); and (3) examination of the duty status, comparing the deployed Army National Guard Unit outcomes to those of an Active Duty participants matched as closely as possible for demographics, MOS, and deployment stress exposures.

KEY RESEARCH ACCOMPLISHMENTS

Vasterling, J.J., Proctor, S. P., Amoroso, P., Kane, R., Gackstetter, G., Ryan, M.A.K., & Friedman, M.J. (2006). The Neurocognition Deployment Health Study: A prospective cohort study of Army soldiers. *Military Medicine, 171*, 253-260.

Vasterling, J.J., Proctor, S. P., Amoroso, P., Kane, R., Heeren, T., & White, R.F. (in press). Neuropsychological Outcomes of Army Personnel Following Deployment to the Iraq War: A Prospective Examination. *Journal of the American Medical Association*.

Vasterling, J. J. & Proctor, S. P. (June, 2003). *Prospective Assessment of Iraq-deployed Troops.* Invited presentation to the Research Advisory Council on Gulf War Veterans Illnesses, Washington, D.C.

Vasterling, J. J. & Proctor, S. P. **(**May, 2003). *Prospective Assessment of Iraq-deploying and Non-deploying Troops: An Interdepartmental Effort.* Invited presentation to the Research Subcommittee of VA/DoD Deployment Health Work Group, Washington, D.C.

Vasterling, J.J., Proctor, S. P., & Kane, R. (October, 2003). *Prospective Assessment of Gulf-deploying and Gulf-nondeploying troops.* Paper presented at the 19th Annual Meeting for the International Society for Traumatic Stress, Chicago, IL.

Vasterling, J. J. (July, 2004). *Prospective Assessment of Psychological and Neuropsychological Functioning in Iraq-deployed Army Troops: A Preliminary Cross-sectional Report.* Invited paper presentation at the VISN 16 MIRECC/National Center for PTSD Summit Meeting, Resilience and Treating Early PTSD, New Orleans, LA.

Proctor, S. P., & Vasterling, J. J. (May, 2004). *Update: From the Gulf War to Operation Iraqi Freedom*. Invited presentation for the USARIEM Environmental Medicine Course 2004, Natick, MA.

Vasterling, J. J. (June, 2005). *Examining the Neuropsychological Outcomes of Iraq Deployment: A Model of Effective DoD/VA Research Collaboration.* Invited presentation at the National Mental Illness Research, Education, and Clinical Center 2005 Conference, New Orleans, LA.

REPORTABLE OUTCOMES

- please see attached *Military Medicine* manuscript
- development of a data-base associated with the NDHS cohort and establishment of the cohort; the data base will facilitate long-term follow-up
- information from the application of the ANAM in this study has been used to inform modification and quality assurance assessment of the ANAM
- planning phase for a VA multi-site cooperative study approved and funded; planning phase in process

CONCLUSIONS

Process Conclusions

This study has established an effective model of inter-departmental collaboration between VA and DoD. This is a critical accomplishment relevant especially to longitudinal research addressing outcomes throughout both military and post-military life periods.

In addition, the work accomplished has provided a model of how neurobehavioral assessments could potentially be incorporated into more regular surveillance with the military. With memory and other cognitive complaints factoring high among war-zone returnees and being of high relevance to occupational functioning and cognitive readiness, the establishment of neurobehavioral surveillance methodology is significant to force health protection efforts. The methods used in this study are non-invasive and could potentially be implemented in a cost-effective manner on a broader scale.

Scientific Conclusions

Findings to date suggest that there are objective changes in neuropsychological functioning associated with deployment. While at least one is at face value positive (improved efficiency in simple reaction time), others are negative (less proficient attentional and memory performances, increased emotional symptoms). Taken together, findings raise the question of a biological stress response, involving neurotransmitter/hormonal systems relevant to the neurobehavioral findings listed above. The design elements of a baseline assessment and of a non-deploying comparison sample well-matched to the deploying sample on key demographic and military characteristics suggest that these findings cannot be attributed solely to pre-existing conditions or simply to the passage of time. The next critical steps will be to examine the secondary outcome, PTSD and the impact of specific risk and resilience factors on the outcomes to determine which individual and deployment-related factors may be serving as critical determinants. The ongoing work will also allow examination of whether these findings are stable over time, if longer-term outcomes can be predicted by early neurobehavioral markers, whether duty status (regular Active Duty versus Guard/Reserve) influences outcomes, and the impact of adverse outcomes on occupational functioning and service utilization with DoD and VA medical care facilities.

REFERENCES

1. Edgar J, Hodgins-Vermaas R, McCartney H, et al: Post-combat syndromes from the Boer War to the Gulf War: a cluster analysis of their nature and attribution. Br Med J 2002; 32: 321-7.

2. Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL: Combat duty in Iraq and Afghanistan: mental health problems and barriers to care. N Eng J Med 2004; 351: 13-22.

Appendix

Please refer to attached *Military Medicine* publication.

The Neurocognition Deployment Health Study: A Prospective Cohort Study of Army Soldiers

Guarantor: Jennifer J. Vasterling, PhD
Contributors: Jennifer J. Vasterling, PhD*†; Susan P. Proctor, DSc‡§¶; COL Paul Amoroso, MC USA¶; Robert Kane, PhD‖#; Col Gary Gackstetter, USAF BSC**; CDR Margaret A. K. Ryan, MC USN††; Matthew J. Friedman, MD PhD‡‡§§

Questions remain regarding the effects of military operational deployment on health. The Neurocognition Deployment Health Study addresses several gaps in the deployment health literature, including lack of baseline health data, reliance on subjective measures of exposure and health variables, prolonged intervals between redeployment and health assessments, and lack of a uniform case definition. The Neurocognition Deployment Health Study uses a prospective cohort design to assess neuropsychological outcomes associated with Iraq deployment. Methods incorporate administration of performance-based neuropsychological measures to Army soldiers before and after Iraq deployment and to nondeployed Army Soldiers assessed during comparable periods of garrison duty. Findings should have the potential to delineate neuropsychological outcomes related to combat theater deployment and to identify potential risk and protective factors related to health outcomes.

Introduction

Unexplained health symptoms appear to be ubiquitous in modern war.[1] However, questions remain regarding linkages between military operational deployment and the development of physical or mental health symptoms. Unresolved issues include whether subjective complaints correspond to objectively measured health indices; whether health problems can be linked to specific environmental exposures, stress exposures, or other deployment-related experiences; and the interaction of deployment with potential risk and resilience factors for health. The Neurocognition Deployment Health Study (NDHS) is a collaboration between the Department of Defense (DoD) and the Department of Veterans Affairs (VA), designed to examine a specific health outcome domain (i.e., neuropsychological functioning) after combat-zone deployment. The study incorporates prospective administration of performance-based measures of neuropsychological functioning to cohorts of Army soldiers deploying in support of Operation Iraqi Freedom. A comparison group of Army Soldiers is assessed before and after an interval of nondeployment.

The primary objectives of this ongoing study are (1) to examine the impact of combat-zone deployment on neuropsychological outcomes, including neurobehavioral and emotional functioning, (2) to examine the impact of deployment-related stress and environmental exposures on neuropsychological outcomes, and (3) to identify potential health risk and protective factors relevant to neuropsychological outcomes. Although post-traumatic stress disorder (PTSD) and depression are measured primarily as potential risk factors for neuropsychological compromise, the study design also permits PTSD and depression screening measures to be treated as outcome variables. Therefore, a secondary objective of the study is to describe select psychiatric outcomes, the importance of which is suggested by high rates of PTSD and other psychiatric disorders after Iraq deployment.[2]

Why Neuropsychological Outcomes?

Neuropsychological functioning encompasses cognitive (e.g., memory, attention, and reasoning), perceptual-sensory-motor (e.g., motor speed), and emotional (e.g., mood) behaviors thought to reflect neural integrity. Much of the deployment health literature stems from the 1991 Gulf War (GW), after which significant subsets of military personnel and veterans reported nonspecific health (e.g., headache and fatigue) and cognitive (e.g., memory impairment) symptoms suggesting possible neural dysfunction.[3-7] For example, 24.1% of individuals in the VA GW Registry Health Examination Program and 36.2% of individuals in the DoD Comprehensive Clinical Evaluation Program complained of memory impairment, making it the fourth most prevalent complaint in both registries.[8] Neuropsychological dysfunction may negatively affect occupational functioning via mechanisms such as reduced performance efficiency, compromised decision-making, distractibility, and increased error rates.[9-14] Therefore, from phenomenological and occupational perspectives, neuropsychological dysfunction is central to the concerns of military personnel.

From a theoretical perspective, certain aspects of neuropsychological functioning would be expected to be sensitive to potential deployment experiences, including neurotoxicant and traumatic stress exposures. The cluster of symptoms reported by some GW returnees overlaps partially with neurotoxic syndromes,[15-17] and recent work revealed that a small

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group of GW participants endorsing health symptoms showed abnormalities on neuroimaging studies.[17] Similarly, emotional sequelae of war-zone stress exposures have been linked to neuropsychological dysfunction among GW veterans.[18-21]

Regarding feasibility, neuropsychological assessments can be conducted without physical discomfort, invasive methods, or expensive technology, rendering neuropsychological assessment a safe, portable, and cost-effective means of estimating neural health. Moreover, neuropsychological functioning can be measured by using standardized, performance-based instruments that facilitate reliable, repeatable, and objective measurements.

Current Gaps in the Deployment Health Literature

Although health problems have been documented after military conflicts dating from the U.S. Civil War,[22] public consciousness regarding war-related illnesses peaked after the 1991 GW. This led to the establishment of DoD and VA clinical health registries[4,23] and, as recommended by the 1994 National Institutes of Health Technology Assessment Workshop,[24] large-scale epidemiological studies examining the effects of GW deployment on health.[3,6,7,25-33] However, much remains unknown about health and military deployment because of limitations of the existing literature, including (1) lack of baseline health data; (2) reliance on subjective, self-report measures of exposure and health outcome variables; (3) health assessments generally conducted long after redeployment (i.e., return from the deployment); and (4) absence of a uniform case definition. The following sections discuss the impact of these issues.

Baseline Functioning

One of the most frequently cited and perhaps most significant obstacles to interpreting health outcome data from the 1991 GW is the lack of information regarding the health of GW veterans before deployment to the Gulf region.[34-36] Without knowledge of baseline health status, it is difficult to determine whether health symptoms reported after redeployment are attributable to deployment or instead reflect preexisting conditions. This problem is exacerbated when self-reported symptoms are "unexplained" because they are not linked to a specific etiology, resulting in potential clinician biases in etiological inference and treatment decisions.[37] The failure to conduct baseline assessments also limits identification of risk and protective factors present before deployment that may moderate the impact of deployment on health outcomes.

In addition to advancing scientific understanding of deployment health issues, accurate chronological attribution of symptom onset and identification of risk and protective factors carry significant administrative and health care policy implications. For example, an understanding of whether specific health conditions were caused or exacerbated by military service potentially affects disability, pension, and compensation decisions within DoD and VA. Similarly, the identification of risk and protective factors holds promise to enhance health outcomes via systems-based prevention programs, when risk can be modified, and via direction of treatment efforts, when risk cannot be modified.

Objective Exposure and Outcome Indices

Exposures

Environmental hazards, psychological stress, and hazard-stress interactions have been proposed as contributors to neuropsychological dysfunction among GW veterans.[38] However, the literature also suggests that neuropsychological and health problems self-reported by deployed GW veterans may not be unique to GW service.[1,5,6,26,39] This controversy centers on incomplete documentation of GW exposures to exogenous health hazards. A number of toxicants have been postulated as etiological factors for GW-related health and cognitive problems, including organophosphate pesticides and chemical warfare agents, solvents, smoke from burning oil wells, and pyridostigmine bromide.[40] However, with rare exceptions (e.g., smoke from oil wells), exposure levels for known toxicants have been difficult to document retrospectively, and some war-zone toxic exposures may remain unknown. Although self-reports have been used in the deployment health literature as proxies for objective exposure data, self-reported GW environmental exposures have proved to be over-reported or unreliable over time.[41,42] As a result, exposure-symptom relationships have been difficult to examine.

Outcomes

Most epidemiological studies examining health outcomes have relied on self-reports of health and cognitive symptoms. Although cognitive impairments (e.g., concentration and memory problems) are among the most common complaints of GW returnees[7,26,30,43] and have distinguished deployed and nondeployed samples,[3] self-reported symptoms do not necessarily correspond to objective measures of neuropsychological functioning. That is, indices of cognitive dysfunction based solely on self-reports are vulnerable to subjective biases and may therefore diverge from performance-based measures.[18,44,45]

Several studies have attempted to address this issue by examining performance on neuropsychological tasks among GW veterans. These efforts yielded inconclusive findings but revealed mild cognitive impairment among some GW subsets. Whereas some studies found that neuropsychological performance deficits among GW veterans were more strongly related to emotional factors than to war-zone variables,[18,19,46,47] others suggested that neuropsychological deficits were associated with illness variables[48-51] and self-reported exposure to war-zone neurotoxicants.[21,52,53] Although inconclusive and subject to the limitations discussed above regarding the lack of baseline and exposure data, such studies point to the potential utility of combining prospectively assessed, objective, neuropsychological data with objectively verified exposure data.

Assessment of Health Outcomes Proximal to Redeployment

Intervals between redeployment and health assessment among GW veterans, with rare exceptions,[54,55] often spanned several years. For example, GW veterans were assessed 4 years after redeployment in the Iowa Persian Gulf Study,[3] 6 years after their return in a large U.K. epidemiological study,[6] 5 years after redeployment in phase I of the National Health Survey of Gulf Era Veterans and Their Families,[7] and 6 years after redeployment in the Canadian GW Forces Study.[27] Although these and

similar studies provide valuable information about some of the longer-term health outcomes of GW veterans and may allow examination of health problems that manifest slowly, a prolonged interval between redeployment and assessment permits the introduction of intervening variables that may also negatively affect health. Furthermore, the health effects of some environmental exposures may dissipate over time and become more difficult to detect as the initial exposure becomes more distant. Therefore, postdeployment health assessments are ideally first conducted soon after redeployment, with repeated assessments to allow detection of more slowly developing conditions.

Lack of Uniform Case Definitions

Attempts to define deployment-related illnesses have often adopted a syndromic approach. However, in the context of unexplained health symptoms following military deployments, such approaches have important limitations. For example, after the 1991 GW, attempts were made to define a syndrome; however, no consistent symptom pattern emerged across individuals or studies.[56] Although certain symptoms (e.g., muscle and joint pain) were commonly reported, no single cluster of symptoms emerged in a consistent manner. Similarly, deployment health researchers defined illness differently across studies, leading to ambiguities regarding the comparability of findings. One potential solution to this problem is to establish a consistent case definition. However, a single-case definition approach may be of limited utility when multiple etiologies are present and multiple biological systems are affected. A second potential approach is to focus on associations between specific exposures and theoretically related outcome domains.

Study Methods

Design

The NDHS uses a prospective cohort design in which Army Soldiers are assessed before Iraq deployment and again within 90 days after redeployment and are compared with nondeployed Army Soldiers assessed once before and once after a comparable period of nondeployment. Because of the continual rotation of forces into the combat theater, it is likely that all military units participating in the study, including nondeploying comparison groups, will eventually deploy. However, study participation of the nondeploying comparison group is limited to a period of garrison duty, and nondeploying units include only those that have not previously deployed to Iraq. Using a modification of the categorization procedure reported by Blood and Aboumrad,[57] the design also includes stratification according to unit type (e.g., combat arms, combat support, or combat service support) and duty status (i.e., active duty or reservist).

Sampling

Sampling is conducted at the battalion unit level, with battalions selected to reflect specific unit types, as described above. The units sampled are anticipated to reflect varying duties, stress exposures, and geographic locations during deployment. The target sample size of 1,550 reflects oversampling of deploying Soldiers (target n = 850), relative to nondeploying Soldiers (target n = 700). The decision to oversample deploying Soldiers was based on power calculations, taking into account planned analyses within the deployed sample that examine the relative impact of deployment-related variables, as well as different attrition rates between the deploying and nondeploying Soldiers. Unit identification is conducted by U.S. Army Forces Command.

Inclusion criteria for individual participants include membership in one of the units identified according to the criteria listed above and willingness to participate. Exclusion criteria include physical injuries or disabilities precluding ability to complete the questionnaires, to see the test stimuli, or to respond to the computer by button-press. Battalion leaders are asked to refer potential participants at random, facilitating inclusion of a representative range of individual ranks, ages, educational backgrounds, and military occupational specialties (MOSs) from each battalion. Refusals and individuals not completing both assessments are tabulated for subsequent analyses of response and longitudinal participation rates.

Measures

Tables I (primary data collection measures) and II (secondary data obtained from military records) provide a summary of the variables to be examined and the sources for obtaining data. Variables fall into three categories, i.e., (1) vulnerability or resilience factors (e.g., previous stress exposure, occupational experience, cognitive readiness, predeployment health status, and health perception), (2) deployment factors (e.g., deployment status, environmental and stress exposures, and duties), and (3) neuropsychological outcomes. The consistent finding that only subgroups of deployed personnel experience health and cognitive impairments after war zone participation emphasizes the need for statistical models that include potential vulnerability and resilience factors as covariates.

Assessment Battery

We attempted to streamline the assessment battery to the degree possible without compromising the major objectives of the work. Although issues of respondent burden are always relevant to data quality, the threshold for overtaxing respondents may be particularly low during preparation for deployment and soon after redeployment. The assessment battery includes a survey of relevant demographic, neuromedical, and historical information; questionnaires assessing stress exposure, emotional distress, and health perception; and performance-based neuropsychological tests. Table I provides a summary of variables derived from the battery.

Survey of Relevant Demographic, Neuromedical, and Historical Information

The Time 1 assessment includes a brief survey recording participant age, handedness, race/ethnicity, gender, education, rank, MOS, deployment and occupational history, and presence or absence of risk factors for neurocognitive dysfunction, including developmental disorders, seizure disorders, head injury, neurotoxicant exposure, and other neurological and medical disorders thought to affect brain functions. In addition, current alcohol and medication consumption, current and historical use of antimalarial medication, and history of emotional or psychiatric disorders are recorded. During the Time 2 assessment, current alcohol and medication usage is reassessed, as is

TABLE I

ASSESSMENT PROTOCOL

Variable	Assessment
Personal history information	
Demographic information, health risk behaviors, military information, neurological and developmental disorders, previous neurotoxicant exposure, diagnosis and treatment history of psychiatric and past alcohol use disorders, current medications, history of head injury, and antimalarial medications	Questionnaire and interview
Stress exposure, deployment risk and resilience factors, emotional distress, and health perception	
Life stress before deployment (DRRI)	Questionnaire
Perception of unit cohesion (DRRI)	
Perception of training as related to preparedness (DRRI)	
Perception of deployment environment (DRRI)	
Life and family concerns (DRRI)	
Deployment concerns (DRRI)	
Combat stress (DRRI)	
Postbattle experiences (DRRI)	
Self-reported exposure to nuclear, biological, and chemical agents (DRRI)	
Perception of health (V/SF12)	
Self-reported cognitive functioning (Medical Outcomes Study CF)	
PTSD symptom severity (PCL)	
State affective disturbance (POMS)	
Depression (CES-D)	
Neurocognitive measures	
WMS Visual Reproductions (visual learning and memory)	Performance-based neuropsychological assessment battery
WMS-III Verbal Paired Associates (verbal learning and memory)	
Trail-Making Test, parts A and B (attention and working memory, respectively)	
NES3 Vocabulary	
NES3 Continuous Performance Test (sustained attention/vigilance)	
ANAM tasks	
Stanford Sleepiness Scale (alertness/sleepiness)	
Simple Reaction Time (processing speed)	
Mathematical Processing (working memory/computational skills)	
Logical Reasoning-Symbolic (grammatical reasoning)	
Code Substitution Learning (learning)	
Code Substitution Delay (memory)	
Running Memory (working memory)	
Tapping (fine motor speed)	
Matching to Sample (visual memory)	
Test of Memory and Malingering	

DRRI, Deployment Risk and Resilience Inventory; V/SF12, Medical Outcomes Study Short Form 12; CF, Cognitive Functioning Scale; PCL, PTSD Checklist; POMS, Profile of Mood States; CES-D, Center for Epidemiological Studies Depression Inventory; WMS, Wechsler Memory Scale; NES3, Neurobehavioral Evaluation System, Ed. 3; ANAM, Automated Neuropsychological Assessment Metrics.

any new development (since Time 1) of emotional disorders or neuromedical risk factors. Verification of this information is obtained from review of available service and medical records, as described below.

Stress Exposures, Emotional Distress, and Health Perception

Stress exposures, emotional distress, and health perception are measured with self-report inventories. However, we also link self-reported stress exposure information to objective indices of combat exposures, as available on a military unit basis. Stress exposures are measured with a modified version of the Deployment Risk and Resilience Inventory,[58] a modular inventory with strong psychometric properties that was developed after the GW to capture events common to contemporary war-zone deployment. State affect and PTSD symptoms are measured during Time 1 and Time 2 assessments with the Profile of Mood States,[59] a 50-item adjective checklist, and the PTSD Checklist,[60] a 17-item checklist that queries for frequency of each of the Diagnostic and Statistical Manual of Mental Disorders, Ed. 4, PTSD diagnostic symptoms. Persistent mood disturbance is measured at Time 2 with the 9-item version of the Center for Epidemiological Studies Depression Inventory.[61,62] Health perception is measured in Time 1 and Time 2 assessments with the Medical Outcomes Study Short Form 12,[63,64] a 12-item scale adapted for use among military veterans and containing somatic and emotional health subscales, and the Medical Outcomes Study Cognitive Functioning Scale,[65] a 4-item scale assessing perception of cognitive functions such as concentration, decision-making, and memory.

Performance-Based Neuropsychological Tests

Administered in its entirety at both Time 1 and Time 2 assessments, the performance-based neuropsychological battery was designed to include (1) measures that might be expected to

TABLE II

MEDICAL AND MILITARY RECORD DATA

Documented medical conditions, immunization history, and hospital and clinic visits
ICD-9-CM-coded diagnoses (for brain and nervous system disorders) from inpatient and outpatient records for the time period starting 1 year (12 months) before the Time 1 assessment through the Time 2 assessment
Anthrax vaccination(s) and date(s) of inoculation
Prescription medication usage and type for the time period between Time 1 and Time 2 assessments
Personal military service history information
Prior military deployment history
Historical rank and occupational specialty information
Armed Forces Qualification Test scores from testing performed upon entry into the service (generally available only for enlisted soldiers)
During-deployment medical surveillance information, i.e., ICD-9-CM-coded diagnoses (for brain and nervous system disorders) documented in theater
Deployment environmental exposure and geographic location information
Environmental exposure data
Unit location information (geographic coordinate information) over time and locale while in theater

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

remain stable in the face of either neurotoxicant or stress exposures, (2) measures sensitive to neurotoxicant exposures, and (3) measures sensitive to stress-related emotional disturbances. The battery was designed to emphasize measurement sensitivity to a greater extent than specificity, and there is some overlap of neuropsychological domains thought to be affected by neurotoxicant exposures and stress (e.g., attention, working memory, and initial acquisition on anterograde memory tests). However, measures were also included (e.g., motor functioning, processing speed, visuospatial processing, and memory retention) that might be expected to differentiate neurotoxic sequelae from those related to psychological distress.

To increase experimenter reliability and to facilitate administration and data management efficiency, most tasks are administered in a computer-assisted format and are drawn primarily from the Automated Neuropsychological Assessment Metrics[66] and the Neurobehavioral Evaluation System, Ed. 3.[67,68] Each of these batteries has undergone considerable psychometric development and has shown acceptable levels of reliability and construct validity.[69–74] Moreover, each contains tasks developed specifically for assessment of the neurocognitive sequelae of hazardous environmental exposures.[75,76] Table I lists Automated Neuropsychological Assessment Metrics and Neurobehavioral Evaluation System subtests included in the assessment battery.

Non-computer-administered, standardized, neuropsychological, performance-based tasks are also included, to allow responses in modalities other than button press (Table I). These include Trail-Making Test parts A and B,[77] Wechsler Memory Scale, 3rd Ed.,[78] Verbal Paired Associates, and Wechsler Memory Scale[79] Visual Reproductions, which were selected because of their sensitivity to neurotoxicant exposures.[80–82] Trial 1 of the Test of Memory and Malingering[83] is administered as an objective index of motivation.

Health and Military Service Record Information

Health Information

Recognizing the important contributions of deployment medical surveillance information to research investigations,[84] we ask participants for permission to request information from medical/health records maintained in DoD computer-based or automated databases. We obtain pharmacy and medical diagnostic information from automated military health care record system databases containing information derived from inpatient and outpatient visits during military service for the period beginning 12 months before the Soldier's study participation and ending with the Time 2 assessment. Also, anthrax vaccination records are requested. We request from the DoD Defense Manpower Data Center Armed Forces Qualification Test scores (as a measure of basic academic skills obtained upon entry into service), personal military deployment history, historical rank, and MOS information (see Table II for a summary of information derived from electronic databases).

Objective Deployment Exposures

Since the 1991 GW, the U.S. Army Center for Health Promotion and Preventive Medicine has collected air, water, and soil measures of various toxicants (i.e., metals, volatile organic compounds, and particulate matter) in areas worldwide where there are U.S. deployment missions. In addition, geographic location information can be used as ancillary data for potential deployment-related experiences and exposures.[85] As indicated in Table II, environmental exposure data and unit geographic location information are acquired from the Center for Health Promotion and Preventive Medicine as available.

Procedures

Informed Consent

Potential participants are briefed individually and undergo consent procedures conducted by civilian study personnel, providing written informed consent before engaging in the study. As part of the consent process, participants are asked if they wish to be contacted again for future studies, allowing for extended longitudinal follow-up monitoring. To protect confidentiality, we do not disclose a Soldier's willingness or refusal to participate to other military personnel, including anyone within the Soldier's unit or chain of command. At each study site, an impartial ombudsman (i.e., someone not connected with the study or in the soldier's chain of command) is available to respond to questions or concerns about the study. Human subject considerations have been reviewed and approved by the Army Surgeon General Human Subjects Research Review Board, the Tulane University Health Sciences Center institutional review board, and local VA committees associated with the principal investigators.

Test Administration

Assessments are conducted at the military installations. The paper-and-pencil questionnaires and neuropsychological tests

are administered by a civilian data collection team, comprised primarily of licensed clinicians and other health care personnel who have completed masters or doctoral level training. The time per participant averages 75 minutes for Time 1 assessments and 85 minutes for Time 2 assessments. The performance-based neuropsychological measures are individually administered, including the computerized measures, which are examiner-assisted. Closed-system headphone sets are used to allow verbal communication between the examiner and study participant while minimizing ambient noise. Paper-and-pencil surveys are completed in small groups (i.e., 8–12 participants).

Data Analysis Plan

Primary research questions will be examined via two approaches. First, we will use repeated-measures multilevel analysis to examine potential interactions addressing whether deployed and nondeployed soldiers differ in baseline and postdeployment measures of neuropsychological functioning. Second, we will use multivariate regression analysis to identify the relative contributions of deployment-related variables (e.g., stress and environmental exposures, unit type, and geographic location) and potential risk factors (e.g., individual difference variables, predeployment health variables, and cognitive performance) to postdeployment outcome measures.

Discussion

Although the past decade has led to increased understanding of possible deployment health effects, considerable gaps in knowledge remain. The ongoing NDHS was initiated in February 2003 to address some of the limitations of past deployment health research, including the absence of prospective health assessments, over-reliance on subjective measures of exposure and outcome variables, prolonged intervals between redeployment and outcomes assessment, and the lack of a uniform case definition.

The NDHS examines neuropsychological functioning before deployment and again after redeployment among Iraq-deploying Army soldiers. The prospective design holds potential to assess changes in neuropsychological functioning over the period of deployment, to identify potential preexisting variables that may serve to increase risk or resilience, and to minimize possible retrospective reporting biases. The postdeployment assessment is conducted within 90 days after redeployment, minimizing the impact of intervening factors developing in the interval between redeployment and assessment and maximizing the sensitivity of the assessment to health problems that develop as a result of deployment exposures that are most potent proximal to their occurrence. Although the current protocol does not extend beyond the initial postdeployment assessment, the cohort design, combined with consent for future assessments, allows for longitudinal extension. Such follow-up monitoring, if conducted, will allow examination of the stability of health outcome measures and the possible longer-term health consequences of deployment.

The inclusion of both deploying and nondeploying groups allows examination of variables related to the passage of time vs. deployment. The nondeploying comparison groups are selected to match, as closely as possible, the deploying study groups in terms of individual and unit military characteristics. It can be speculated that most of the nondeploying units included in the study will also eventually deploy. However, their study participation is limited to assessment before and after a period of garrison duty, thus allowing them to serve initially as an appropriate nondeployed comparison sample. The inclusion within groups (deployed and nondeployed) of different unit types (combat arms, combat support, and combat service support) will likely allow variations in both the geographic distribution and types of missions performed by Soldier participants during Iraq deployment. The inclusion of both regular active duty and reservist Soldiers increases the representativeness of the sample for the larger Iraq-deploying military population and allows examination of duty type as a predictive variable.

The choice of neuropsychological functioning as a primary outcome focus reflects consideration of several factors. First, the neuropsychological outcome domain has a theoretical and phenomenological basis relative to deployment health effects and the biological systems that may be affected by hypothesized deployment-related exposures. Second, neuropsychological impairment has significant implications for occupational functioning. Finally, neuropsychological functioning can be measured with objective, performance-based measures that are portable and cost-effective. The secondary mental health outcome domain reflects disorders (i.e., PTSD and depression) highly likely to develop following stress exposures associated with Iraq deployment[2] and linked to neuropsychological dysfunction in military veteran[86–89] and civilian[90–93] samples. The inclusion of objective environmental exposure data will help address past gaps in the literature related to failure to document or to verify possible hazardous environmental and occupational exposures.

In summary, this ongoing study, although restricted to a somewhat narrow range of health outcomes, addresses some of the gaps in knowledge inherent to the existing deployment health literature. It is the first relatively large-scale effort to assess deployment health using a prospective cohort design with primary data collection of objective outcome measures. It is hoped that the findings of this study will complement those produced by large, prospective, survey-based, cohort studies such as the Millennium Cohort Study.[94] The NDHS also serves as an additional model of successful DoD-VA collaboration and of prospective primary data collection of health-related outcomes. Future research will build on this effort by including other service branches, examining additional outcomes, and extending the longitudinal assessment beyond a single follow-up assessment.

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References

1. Edgar J, Hodgins-Vermaas R, McCartney H, et al: Post-combat syndromes from the Boer War to the Gulf War: a cluster analysis of their nature and attribution. Br Med J 2002; 32: 321–7.
2. Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL: Combat duty in Iraq and Afghanistan: mental health problems and barriers to care. N Engl J Med 2004; 351: 13–22.
3. Iowa Persian Gulf Study Group: Self-reported illness and health status among Gulf War veterans. JAMA 1997; 277: 238–45.
4. Joseph SC, Comprehensive Clinical Evaluation Program Team: A comprehensive clinical evaluation of 20,000 Gulf War veterans. Milit Med 1997; 162: 149–55.
5. Ismail K, Everitt B, Blatchely N, et al: Is there a Gulf War syndrome? Lancet 1999; 353: 179–82.
6. Unwin C, Blatchley N, Coker W, et al: Health of U.K. servicemen who served in the Persian Gulf War. Lancet 1999; 353: 169–78.
7. Kang HK, Mahan CM, Lee KY, Magee CA, Murphy FM: Illnesses among United States veterans of the Gulf War: a population-based survey of 30,000 veterans. J Occup Environ Med 2000; 42: 491–501.
8. Department of Veterans Affairs, Veterans Health Administration and Department of Defense, Office of the Assistant Secretary of Defense, Health Affairs: Combined Analysis of the Veterans Affairs and Department of Defense Gulf War Clinical Evaluation Programs: A Study of the Clinical Findings from Systematic Medical Examinations of 100,339 U.S. Gulf War Veterans. Washington, DC, Department of Defense, 2002.
9. Poulton EC, Hunt GM, Carpenter A, Edwards RS: The performance of junior hospital doctors following reduced sleep and long hours of work. Ergonomics 1978; 21: 279–95.
10. Angus RG, Helsegrave RJ: Effects of sleep loss on sustained cognitive performance during a command and control simulation. Behav Res Methods Instrum Comput 1985; 17: 55–67.
11. Rosa RR, Colligan MJ, Lewis P: Extended workdays: effects of 8-hour and 12-hour rotating shift schedules on performance, subjective alertness, sleep patterns, and psychosocial variables. Work Stress 1989; 3: 21–32.
12. Rubin R, Orris P, Lau SL, Hryhorczuk DO, Furner S, Letz R: Neurobehavioral effects of the on-call experience in housestaff physicians. J Occup Med 1991; 33: 13–8.
13. Proctor SP, White RF, Robins TG, Echeverria D, Rocskay AZ: The effect of overtime work on cognitive function in automotive workers. Scand J Work Environ Health 1996; 22: 124–32.
14. Lieberman HR, Tharion WJ, Shukitt-Hale B, Speckman KL, Tulley R: Effects of caffeine, sleep loss, and stress on cognitive performance and mood during U.S. Navy SEAL training. Psychopharmacology 2002; 164: 250–61.
15. Haley RW, Kurt TL: Self-reported exposure to neurotoxic chemical combinations in the Gulf War: a cross-sectional epidemiologic study. JAMA 1997; 277: 231–7.
16. Flaxman NA: Gulf War illness: does anticholinesterase exposure play a role? Fed Pract 1999; 16: 13–6.
17. Haley RW, Fleckenstein JL, Marshall WW, McDonald GG, Kramer GL, Petty F: Effect of basal ganglia injury on central dopamine activity in Gulf War syndrome: correlation of proton magnetic resonance spectroscopy and plasma homovanillic acid levels. Arch Neurol 2000; 57: 1280–5.
18. Axelrod BN, Milner IB: Neuropsychological findings in a sample of Operation Desert Storm veterans. J Neuropsychiatry Clin Neurosci 1997; 9: 23–8.
19. Sillanpaa MC, Agar LM, Milner IB, Podany EC, Axelrod BN, Brown GG: Gulf War veterans: a neuropsychological examination. J Clin Exp Neuropsychol 1997; 19: 211–9.
20. Vasterling JJ, Brailey K, Constans JI, Sutker PB: Attention and memory dysfunction in posttraumatic stress disorder. Neuropsychology 1998; 12: 125–33.
21. Lindem K, Heeren T, White RF, et al: Neuropsychological performance in Gulf War-era veterans: traumatic stress symptomatology and exposure to chemical-biological warfare agents. J Psychopathol Behav Assess 2003; 25: 105–20.
22. Hyams KC, Wignall FS, Roswell R: War syndromes and their evaluation: from the U.S. Civil War to the Persian Gulf War. Ann Intern Med 1996; 125: 398–405.
23. Murphy FM, Kang H, Dalager NA, et al: The health status of Gulf War veterans: lessons learned from the Department of Veterans Affairs Health Registry. Milit Med 1999; 164: 327–31.
24. National Institutes of Health Technology Assessment Workshop Panel: The Persian Gulf experience and health. JAMA 1994; 272: 391–6.
25. Stretch RH, Bliese PD, Marlow DH, Wright KM, Knudson KH, Hoover CH: Physical health symptomatology of Gulf War-era service personnel from the state of Pennsylvania and Hawaii. Milit Med 1995; 160: 131–6.
26. Fukuda K, Nisenbaum R, Stewart G, et al: Chronic multisymptom illness affecting Air Force veterans of the Gulf War. JAMA 1998; 280: 981–8.
27. Goss Gilroy, Inc: Health Study of Canadian Forces Personnel Involved in the 1991 Conflict in the Persian Gulf, Vol I. Ottawa, Ontario, Canada, Department of Defense, 1998.
28. Wolfe J, Proctor S, Davis JD, Sullivan M, Friedman M: Health symptoms reported by Gulf War veterans two years after return. Am J Ind Med 1998; 33: 104–13.
29. Gray GC, Kaiser KS, Hawksworth AW, Hall FW, Barrett-Connor E: Increased post-war symptoms and psychological morbidity among U.S. Navy Gulf War veterans. Am J Trop Med Hyg 1999; 60: 758–66.
30. Ishoy T, Suadicani P, Guldager B, Appleyard M, Hein H, Gyntelberg F: State of health after deployment in the Persian Gulf: the Danish Gulf War study. Dan Med Bull 1999; 46: 416–9.
31. Doebbeling BN, Clarke WR, Watson D, et al: Is there a Persian Gulf War syndrome? Results from a large population-based survey of deployed veterans and nondeployed controls. Am J Med 2000; 108: 695–704.
32. Steele L: Prevalence and patterns of Gulf War illness in Kansas veterans: associations of symptoms and characteristics of person, place, and time of military service. Am J Epidemiol 2000; 152: 992–1002.
33. Cherry N, Creed F, Silman A, et al: Health and exposures of United Kingdom Gulf War veterans, part I: the pattern and extent of ill health. Occup Environ Med 2001; 58: 291–8.
34. Persian Gulf Veterans Coordinating Board: Unexplained illnesses among Desert Storm veterans: a search for causes, treatment, and cooperation. Arch Intern Med 1995; 155: 262–8.
35. Riddle JR, Hyams KC, Murphy FM, Mazzuchi JF: In the borderland between health and disease following the Gulf War. Mayo Clin Proc 2000; 75: 777–9.
36. Hyams KC, Barrett DH, Dugue D, et al: The Recruitment Assessment Program: a program to collect comprehensive baseline health data from U.S. military personnel. Milit Med 2002; 167: 44–7.
37. Richardson RD, Engel CC, McFall M, McKnight K, Boehnlein JK, Hunt SC: Clinician attributions for symptoms and treatment of Gulf War-related health concerns. Arch Intern Med 2001; 161: 1289–94.
38. Presidential Advisory Committee on Gulf War Veterans' Illnesses: Final Report. Washington, DC, U.S. Government Printing Office, 1996.
39. Murphy FM: Gulf War syndrome: there may be no specific syndrome, but troops suffer after most wars. Br Med J 1999; 318: 274–5.
40. Joseph SC, Hyams KC, Gackstetter GD, Matthews EC, Patterson RE: Persian Gulf War health issues. In: Environmental and Occupational Medicine, Ed 3, pp 1595–1610. Edited by Rom WN. Philadelphia, PA, Lippincott-Raven, 1998.
41. McCauley LA, Joos SK, Spencer PS, Lasarev M, Shuell T, Portland Environmental Hazards Research Center: Strategies to assess validity of self-reported exposures during the Persian Gulf War. Environ Res 1999; 81: 195–205.
42. Wessely S, Unwin C, Hotopf M, et al: Stability of recall of military hazards over time. Br J Psychiatry 2003; 183: 314–22.
43. Proctor SP, Heeren T, White RF, et al: Health status of Persian Gulf War veterans: self-reported symptoms, environmental exposures, and the effect of stress. Int J Epidemiol 1998; 27: 1000–10.
44. Binder LM, Storzbach D, Anger WK, Campbell KA, Rohlman DS, Portland Environmental Hazards Research Center: Subjective cognitive complaints, affective distress, and objective cognitive performance in Persian Gulf War veterans. Arch Clin Neuropsychol 1999; 14: 531–6.
45. David AS, Farrin L, Hull L, Unwin C, Wessely S, Wykes T: Cognitive functioning and disturbances of mood in U.K. veterans of the Persian Gulf War: a comparative study. Psychol Med 2002; 32: 1357–70.
46. Goldstein G, Beers SR, Morrow LA, Shemanski WJ, Steinhauer SR: A preliminary neuropsychological study of Persian Gulf War veterans. J Int Neuropsychol Soc 1996; 2: 368–71.
47. Vasterling JJ, Brailey K, Tomlin H, Rice J, Sutker PB: Olfactory functioning in Gulf War-era veterans: relationships to war-zone duty, self-reported hazards exposures, and psychological distress. J Int Neuropsychol Soc 2003; 9: 407–18.
48. Hom J, Haley RW, Kurt TL: Neuropsychological correlates of Gulf War syndrome. Arch Clin Neuropsychol 1997; 12: 531–44.
49. Anger WK, Storzbach D, Binder LM, et al: Neurobehavioral deficits in Persian Gulf veterans: evidence from a population-based study. J Int Neuropsychol Soc 1999; 5: 203–12.
50. Binder LM, Storzbach D, Campbell KA, Rohlman DS, Anger WK, Portland Environmental Hazards Research Center: Neurobehavioral deficits associated with chronic fatigue syndrome in veterans with Gulf War unexplained illnesses. J Int Neuropsychol Soc 1999; 7: 835–9.

51. Lang G, Tiersky LA, DeLuca J, et al: Cognitive functioning in Gulf War illness. J Clin Exp Neuropsychol 2001; 23: 240–9.
52. White RF, Proctor SP, Heeren T, et al: Neuropsychological function in Gulf War veterans: relationships to self-reported toxicant exposures. Am J Ind Med 2001; 40: 42–54.
53. Sullivan K, Krengel M, Proctor SP, Devine S, Herren T, White RF: Cognitive functioning in treatment-seeking Gulf War veterans: effects of acute stress reactions and pyridostigmine bromide. J Psychopathol Behav Assess 2003; 25: 95–104.
54. Wolfe J, Kelley J, Buscela M, Mark W: Fort Devens Reunion Survey: report of phase I. In: Returning Persian Gulf Troops: First Year Findings, pp 19–44. Edited by Rosenheck R, Becnel H, Blank A. New Haven, CT, Department of Veterans Affairs, 1992.
55. Wolfe J, Brown P, Kelley J: Reassessing war stress: exposure and the Gulf War. J Soc Issues 1993; 49: 15–31.
56. Barrett DH, Gray GC, Doebbeling BN, Clauw DJ, Reeves WC: Prevalence of symptoms and symptom-based conditions among Gulf War veterans: current status of research findings. Epidemiol Rev 2002; 24: 218–27.
57. Blood CG, Aboumrad TL: A comparison of postdeployment hospitalization incidence between active duty Vietnam and Persian Gulf War veterans. Milit Med 2001; 166: 648–55.
58. King DW, King LA, Vogt DS: Manual for the Deployment Risk and Resilience Inventory (DRRI): A Collection of Measures for Studying Deployment-Related Experiences of Military Veterans. Boston, MA, National Center for PTSD, 2003.
59. McNair DM, Lorr M, Droppelman LF: Profile of Mood States. San Diego, CA, Educational and Industrial Testing Service, 1971.
60. Weathers FW, Huska JA, Keane TM: The PTSD Checklist, Military Version (PCL-M). Boston, MA, National Center for PTSD, 1991.
61. Radloff LS: The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Measure 1977; 1: 385–401.
62. Santor DA, Coyne JC: Shortening the CES-D to improve its ability to detect cases of depression. Psychol Assess 1997; 9: 233–43.
63. Ware JE, Kosinski M, Keller SD: A 12-item short form health survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996; 34: 220–33.
64. Kazis LE, Ren XS, Lee A, et al: Health Status and Outcomes of Veterans: Physical and Mental Component Summary Scores (Veterans SF-12): 1998 National Survey of Hospitalized Patients, Executive Report. Washington, DC, Office of Performance and Quality, Health Assessment Project, Health Services Research and Development Field Program, 1999.
65. Stewart AL, Ware JE, Sherbourne CD, Wells KB: Psychological distress/well-being and cognitive functioning measures. In: Measuring Functioning and Well-Being: The Medical Outcomes Study Approach, pp 102–42. Edited by Stewart AL, Ware JE. Durham, NC, Duke University, 1992.
66. Reeves D, Kane R, Elsmore T, Winter K, Bleiberg J: ANAM2001 User's Manual: Clinical and Research Modules. Special report NCRF-SR-2002-1. San Diego, CA, National Cognitive Recovery Foundation, 2002.
67. Letz R, Green RC, Woodward JL: Development of a computer-based battery designed to screen adults for neuropsychological impairment. Neurotoxicol Teratol 1996; 18: 365–70.
68. Letz R: NES3 User's Manual. Atlanta, GA, Neurobehavioral Systems, 2000.
69. Gastaldo E, Reeves D, Levinson D, Betsinger K, Winger B: ANAM USMC Normative Data, Series I: The Effects of Heat Stress on Neurocognitive Function. Technical report NCRF-TR-96-01. San Diego, CA, National Cognitive Recovery Foundation, 1996.
70. Letz R, Pieper WA, Morris R: NES test performance in a large U.S. Army veteran sample: relationships with both demographic factors and traditional neuropsychological tests. Neurotoxicol Teratol 1996; 18: 381–90.
71. Retzlaff P, Vanderploeg RD: Validity Study of the S-CAT: Final Report for MS80,665. Houston, TX, Medical Operations Branch, NASA, Lyndon B. Johnson Space Center, 1999.
72. Bleiberg J, Kane RL, Reeves DL, Garmoe WS, Halpern E: Factor analysis of computerized and traditional tests used in mild brain injury research. Clin Neuropsychol 2000; 14: 287–94.
73. Kabat MH, Kane RL, Jefferson AL, DiPino RK: Construct validity of selected Automated Neuropsychological Assessment Metrics (ANAM) battery measures. Clin Neuropsychol 2001; 15: 498–507.
74. Letz R, Dilorio CK, Shafer PO, Yeager KA, Schomer DL, Henry TR: Further standardization of some NES3 tests. Neurotoxicology 2003; 24: 491–501.
75. Letz R: The Neurobehavioral Evaluation System: an international effort. In: Advances in Behavioral Toxicology, pp 189–201. Edited by Johnson B. Chelsea, MI, Lewis Publishers, 1990.
76. Kane RL, Kay GG: Computerized assessment in neuropsychology: a review of tests and test batteries. Neuropsychol Rev 1992; 3: 1–117.
77. Reitan RM: Validity of the Trail Making Test as an indication of organic brain damage. Percept Mot Skills 1958; 8: 271–6.
78. Wechsler DA: Wechsler Memory Scale, Ed 3. San Antonio, TX, Psychological Corp, 1997.
79. Wechsler DA: A standardized memory scale for clinical use. J Psychol 1945; 19: 87–95.
80. White RF, Feldman RG, Travers PH: Neurobehavioral effects of toxicity due to metals, solvents, and insecticides. Clin Neuropharmacol 1990; 13: 392–412.
81. Echeverria D, White RF, Sampio C: A behavioral evaluation of PCE exposure in patients and dry cleaners: a possible relationship between clinical and preclinical effects. J Occup Environ Med 1995; 37: 667–80.
82. White RF: Patterns of neuropsychological impairment associated with neurotoxicants. Clin Occup Environ Med 2001; 1: 577–93.
83. Tombaugh TN: Test of Memory and Malingering. North Tonawanda, NY, Multi-Health Systems, 1996.
84. Rubertone MV, Brundage JF: The Defense Medical Surveillance System and the Department of Defense Serum Repository: glimpses of the future of public health surveillance. Am J Public Health 2002; 92: 1900–4.
85. Proctor SP, Gopal S, Imai A, Wolfe J, Ozonoff D, White RF: Spatial analysis of 1991 Gulf War troop locations in relationship with post-war health symptom reports using GIS techniques. Trans GIS 2005; 9: 381–96.
86. Bremner JD, Scott TM, Delaney RC, et al: Deficits in short-term memory in posttraumatic stress disorder. Am J Psychiatry 1993; 150: 1015–9.
87. Yehuda R, Keefe RSE, Harvey PD, et al: Learning and memory in combat veterans with posttraumatic stress disorder. Am J Psychiatry 1995; 152: 137–9.
88. Gilbertson MW, Gurvits TV, Lasko NB, Orr SP, Pitman RK: Multivariate assessment of explicit memory function in combat veterans with posttraumatic stress disorder. J Trauma Stress 2001; 14: 413–32.
89. Vasterling JJ, Duke LM, Brailey K, Constans JI, Allain AN, Sutker PH: Attention, learning, and memory performance and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. Neuropsychology 2002; 16: 5–14.
90. Burt DB, Zembar MJ, Niederehe G: Depression and memory impairments: a meta-analysis of the association, its pattern, and specificity. Psychol Bull 1995; 117: 285–305.
91. Veiel HOF: A preliminary profile of neuropsychological deficits associated with major depression. J Clin Exp Neuropsychol 1997; 19: 587–603.
92. Jenkins MA, Langlais PJ, Delis D, Cohen R: Learning and memory in rape victims with posttraumatic stress disorder. Am J Psychiatry 1998; 155: 278–9.
93. Brandes D, Ben-Schachar G, Gilboa A, Bonne O, Freedman S, Shalev AY: PTSD symptoms and cognitive performance in recent trauma survivors. Psychiatry Res 2002; 110: 231–8.
94. Gray GC, Chesbrough KB, Ryan MAK, et al: The Millennium Cohort Study: a 21-year prospective cohort study of 140,000 military personnel. Milit Med 2002; 167: 483–8.